NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ixazomib with lenalidomide and dexamethasone in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers). [Add link to website in-development page on 'committee papers']

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: August 2017

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using ixazomib with lenalidomide and dexamethasone in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 26 September 2017

Second appraisal committee meeting: to be confirmed

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Ixazomib, with lenalidomide and dexamethasone, is not recommended within its marketing authorisation for treating multiple myeloma in adults who have already had at least 1 therapy.

1.2 This recommendation is not intended to affect treatment with ixazomib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Ixazomib (with lenalidomide and dexamethasone) has a marketing authorisation to treat multiple myeloma in people who have had 1 or more previous therapies. But it is likely to be used only for people who have had 2 or 3 previous therapies.

The main clinical trial is ongoing and limited data are available. It is not yet clear whether ixazomib prolongs life compared with the current treatment for people who have had 2 or 3 therapies (lenalidomide plus dexamethasone).

Ixazomib did not meet NICE's criteria to be considered as a life-extending treatment at the end of life. For people who have had 2 or 3 therapies, the minimum estimate of cost effectiveness varied between £125,000 and £274,000 per quality-adjusted life year gained compared with current treatment, but was closer to the upper estimate. This is much higher than what NICE normally considers an acceptable use of NHS resources, so ixazomib cannot be recommended.

For ixazomib to be included in the Cancer Drugs Fund the company proposed a price reduction, which reduces the cost-effectiveness estimates. However ixazomib is still unlikely to be cost effective at the proposed price. Therefore it is not suitable for use within the Cancer Drugs Fund.

2 The technology

Ixazomib citrate (Ninlaro, Takeda)	
Marketing authorisation	'Ninlaro in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have had at least 1 previous therapy'.
Recommended dose and schedule	Capsules, 4 mg once a week on days 1, 8, and 15 of a 28-day cycle. Taken with lenalidomide 25 mg daily on days 1 to 21 of the cycle and dexamethasone 40 mg on days 1, 8, 15, and 22 of the cycle.
Price	£6,336 per cycle (3 capsules, excluding VAT; NHS Dictionary of Medicines and Devices [accessed April 2017]). Takeda agreed a simple patient access scheme with the Department of Health, which was considered in the development of this guidance. The details of this patient access scheme are commercial in confidence. The company also proposed a commercial offer for use of ixazomib in the Cancer Drugs Fund (CDF).

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Takeda and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

New treatment option

People with multiple myeloma will welcome a new treatment option

3.1 The patient experts explained that multiple myeloma is an incurable cancer characterised by multiple relapses, and patients would appreciate an additional option to extend the treatment pathway. The patient and clinical experts emphasised that oral treatment regimens are very important, especially for older and frail patients. The committee concluded that people would welcome new oral treatment options for multiple myeloma.

Combining an immunomodulatory agent with a proteasome inhibitor is an important development in multiple myeloma treatment

3.2 The clinical experts explained that triple therapy regimens combining a proteasome inhibitor (such as ixazomib) with an immunomodulatory agent (such as lenalidomide) are becoming the standard of care for multiple myeloma. They explained that this is because of the synergistic effect of combining drugs with different mechanisms of action, which is particularly relevant later in the treatment pathway when multiple myeloma cells develop resistance to treatment. The clinical experts noted that the only available triple therapy regimen which combines a proteasome inhibitor with an immunomodulatory agent is bortezomib with thalidomide and dexamethasone, which is associated with severe side effects. The committee concluded that new triple therapy combinations with improved tolerability and more convenient administration would be welcomed.

People with multiple myeloma value longer periods between relapses

3.3 The patient expert explained that being progression-free is important to patients, both psychologically and physically. They also explained that a relapse of multiple myeloma, even without symptoms (known as biochemical progression), causes anxiety and affects daily activities. The clinical experts noted that progression-free survival is an important outcome for patients because relapses can be fatal, especially in older people. The committee concluded that progression-free survival is important to people with multiple myeloma.

Clinical management

People who have had 1 previous treatment with bortezomib have limited treatment options

3.4 The committee understood that first-line treatment options for multiple myeloma differ depending on whether stem cell transplant is appropriate. Bortezomib plus dexamethasone, with or without thalidomide, is given as an induction therapy before stem cell transplant. If stem cell transplant is

not suitable, thalidomide or bortezomib is offered (with melphalan and prednisone). The committee was aware that people who have had 1 treatment with thalidomide have bortezomib plus dexamethasone as second-line treatment. People who have had 1 treatment with bortezomib used to be offered retreatment with bortezomib or with lenalidomide plus dexamethasone through the Cancer Drugs Fund, but these are no longer available. The committee agreed that bortezomib retreatment, or lenalidomide plus dexamethasone, is not established practice in the NHS for people who have had 1 previous therapy. It noted that the NICE scope does not include any other treatment options as comparators. The committee heard from a clinical expert that there is a gap at this point in the treatment pathway and, because there are no other options, cytotoxic chemotherapy is offered (such as cyclophosphamide plus thalidomide and dexamethasone). However, there are no clinical data supporting cytotoxic chemotherapy at this point in the pathway. The committee concluded that people who have had 1 previous treatment with bortezomib have limited treatment options at first relapse.

Lenalidomide plus dexamethasone is used after 2 or 3 previous therapies

3.5 The clinical experts explained that, in current practice in England, lenalidomide plus dexamethasone is mainly used for people who have had 2 previous therapies. It can also be used for people who have had 3 previous therapies provided that they have not had lenalidomide before. The committee noted that this was supported by market share data submitted by the company. These data showed that lenalidomide plus dexamethasone is the most common treatment for people who have had 2 previous therapies (69% of people) and that 25% of people who have had 3 or more previous therapies have lenalidomide plus dexamethasone. The clinical experts explained that many people in multiple myeloma clinical trials have not had lenalidomide as one of their 3 previous lines of therapy, and are therefore offered lenalidomide plus dexamethasone as their fourth treatment. The committee concluded that lenalidomide plus

dexamethasone is established clinical practice for treating multiple myeloma in people who have had 2 or 3 previous therapies.

Panobinostat is mainly used only after 3 previous therapies

3.6 NICE's technology appraisal guidance on panobinostat for treating multiple myeloma recommends panobinostat plus bortezomib and dexamethasone for people who have had at least 2 previous therapies including bortezomib and an immunomodulatory agent. But the committee heard from the clinical experts that the panobinostat regimen is used later in the treatment pathway, because it is associated with toxic side effects and a complicated dosing regimen. The clinical experts stated that they would always prefer to use lenalidomide before panobinostat, which the company stated was supported by market research data, and therefore panobinostat is not used unless people have had 3 therapies. The committee heard from the clinical experts that panobinostat is sometimes reserved until later in the pathway, after 4 previous therapies, instead of bendamustine. The committee concluded that the panobinostat regimen is mainly used only after 3 previous therapies, one of which usually includes lenalidomide.

Expected use of ixazomib

The main use is for people who have had 2 or 3 previous therapies

3.7 The company submission included analyses for people who have had 1 previous therapy and for people who have had 2 or 3 previous therapies. The committee heard from the clinical experts that ixazomib (plus lenalidomide and dexamethasone) would be used in the same place in the pathway that lenalidomide plus dexamethasone is currently used; that is, for people who have had 2 or 3 previous therapies (see section 3.5). The committee noted uncertainties about the relevant comparators for people who have had 1 previous therapy:

- The company submission included only 1 comparator for people who have had 1 previous therapy: bortezomib plus dexamethasone. The committee recalled that this comparator is only relevant for people who have had thalidomide, whereas for people who have had bortezomib the comparator is a cyclophosphamide-based regimen (see section 3.4). A comparison with cyclophosphamide is not possible because there are no data for it in this population. Because of this, and advice from experts that ixazomib is not expected to be widely used in people who have had 1 previous therapy, NICE did not re-issue the scope to include cyclophosphamide as a comparator.
- A review of the NICE technology appraisal guidance for lenalidomide plus dexamethasone in this population is ongoing.

At its first meeting the committee agreed to consider the analysis in people who have had 1 previous therapy because this population is included in the marketing authorisation, and the company presented some evidence for it. But in response to consultation, the company stated that it did not wish to pursue a recommendation for this population because of the uncertainties about comparators. The company did not include analyses for people who have had 1 previous therapy in the additional evidence it submitted after the first committee meeting. The committee concluded that it would focus its discussion on people who have had 2 or 3 previous therapies because this reflects the expected use of ixazomib in clinical practice.

Comparators

After 2 or 3 previous therapies, the comparator is lenalidomide plus dexamethasone

3.8 The company submission included a comparison with lenalidomide plus dexamethasone for people who have had 2 or 3 previous therapies. The committee agreed that this was appropriate and reflected clinical practice in England. The committee was aware that panobinostat with bortezomib

and dexamethasone is also an option for people who have had 3 therapies, but recalled that panobinostat is normally used after lenalidomide (see section 3.6). Therefore, it understood that panobinostat would be used only after ixazomib (which is given with lenalidomide and dexamethasone). The committee concluded that it was not relevant to compare ixazomib with panobinostat.

Clinical effectiveness

Ixazomib improves progression-free survival after 2 or 3 previous therapies

3.9 The TOURMALINE-MM1 (TMM1) trial of ixazomib is ongoing. TMM1 is comparing ixazomib (plus lenalidomide and dexamethasone) with lenalidomide plus dexamethasone. The results of 2 interim analyses are available. The company used the results of the most recent interim analysis in its updated model, submitted after consultation. The primary endpoint of TMM1 is progression-free survival, which the committee acknowledged was an important outcome for people with multiple myeloma (see section 3.3). The committee was aware that data from the second interim analysis showed a reduced benefit of ixazomib on progression-free survival in the intention-to-treat population; the difference between treatment arms was statistically significant at the first but not the second interim analysis. But the committee noted that for people who had 2 or 3 previous therapies, the difference between treatment arms in median progression-free survival was statistically significant in both interim analyses; at the second interim analysis the difference was 9 months (p=0.003). It heard during consultation that this difference was clinically meaningful. The committee concluded that ixazomib improves progression-free survival after 2 or 3 prior therapies.

The survival benefit of ixazomib is uncertain

3.10 The committee noted that median overall survival was not reached in either arm of the TMM1 trial, and that the marketing authorisation for ixazomib is conditional on the company providing additional clinical data,

including more mature survival results. The clinical experts stated that they would expect to see a survival benefit with ixazomib after longer follow-up, but the committee concluded that the current data are too immature to make a reliable conclusion about overall survival.

Differences in prognostic patient characteristics explain why ixazomib appears to be more effective after 3 previous therapies than after 2 previous therapies

3.11 TMM1 stratified patients according to the number of treatments they had before the trial, resulting in 2 pre-specified subgroups: people who have had 1 previous therapy and people who have had 2 or 3 previous therapies. At its first meeting, the committee concluded that the benefit of ixazomib in the subgroup who had 2 or 3 previous therapies might be driven by favourable results in the patients who had 3 previous therapies, according to an analysis from the ERG of overall survival, progression-free survival and overall response rates. The company had stated that it was inappropriate to consider the results from people who have had 3 previous therapies separately to the results from people who have had 2 previous therapies. This is because it breaks the randomisation of the trial, which was stratified according to number of previous therapies (1 and 2 or 3). The company explained that people who had 3 previous therapies had major differences in prognostic baseline characteristics compared with people who had 2 previous therapies, which may have artificially increased the treatment benefit seen with ixazomib in people who had 3 previous therapies. The company provided evidence to support this during consultation, and the ERG agreed with the company's explanation. The committee concluded that the differences in prognostic baseline characteristics explain why ixazomib appears to be more effective after 3 previous therapies than after 2 previous therapies, and it did not need to separately consider people who had 2 previous therapies.

Clinical evidence in the economic model

It is appropriate to use the data after 2 or 3 previous therapies to compare ixazomib with lenalidomide

3.12 The data in the model, for the comparison with lenalidomide plus dexamethasone, was based on people who had 2 or 3 previous therapies. The committee agreed that this was appropriate because both ixazomib and lenalidomide could be used for people who had 2 previous therapies and for those who had 3 previous therapies.

Extrapolating clinical trial data in the economic model

The relative benefit of ixazomib is unlikely to be maintained for a person's lifetime

3.13 The company model assumed that the relative survival benefit of ixazomib in the clinical trial, compared with lenalidomide plus dexamethasone, is maintained at the same level indefinitely. The company justified its approach because the trial data supported the assumption of proportional hazards. However, the committee noted that the proportional hazards assumption is proven for only the 23-month median trial follow-up period (that is, the relative benefit of ixazomib is constant for 23 months), and there is no evidence about what happens after this. The committee agreed that it was unlikely that the relative benefit of ixazomib would be maintained undiminished for the rest of a patient's life, and it had not seen evidence to support this for other treatments. It heard from 1 clinical expert that the relative benefit was likely to be maintained for at least 1 or 2 further relapses, diminishing over a period of about 2 years. The committee concluded that the duration of the relative treatment benefit of ixazomib after stopping treatment is uncertain but, based on the committee's experience appraising immunomodulatory therapies for treating cancer, the survival benefit of ixazomib would be unlikely to continue for a period beyond 5 years.

There is uncertainty about the best way to extrapolate the trial data

3.14 The ERG explained that the company's approach to extrapolating the progression-free survival data beyond the observed trial data (using a generalised gamma model) resulted in more people alive with un-progressed disease than the total number of people alive in the updated model, which is not possible. The ERG noted that the company's method of correcting this in the model produced clinically implausible results because it assumed that no one survives after disease progression. The ERG explained that more plausible results are achieved by using the Weibull curve to extrapolate progression-free survival and time-on-treatment (instead of the generalised gamma and exponential, respectively), and the Gompertz curve to extrapolate overall survival (instead of the Weibull curve). The committee was aware that this approach increased the incremental cost-effectiveness ratio (ICER) substantially, because the expected incremental survival gain with ixazomib reduced (from an increase of 1.56 years compared with lenalidomide plus dexamethasone, to an increase of 0.99 years). The ERG noted that the mortality predicted using the Gompertz curve (less than 10% of patients alive after 10 years) is higher than with the other curves. The committee considered that the Gompertz curve more accurately reflected the prognosis of people who have already had 2 or 3 previous therapies. But it heard from the company that the Weibull curve was a better representation of the observed data than the Gompertz curve. The ERG explained that using the Gompertz curve to extrapolate overall survival has a similar effect to applying a diminishing relative treatment effect for ixazomib, and that doing both would underestimate the survival benefit of ixazomib. On balance, the committee concluded that the company's curves could be considered for decision-making as long as a diminishing treatment effect for ixazomib, relative to lenalidomide, was applied to the model (see section 3.13).

Health-related quality of life

Utility estimates from both the company and the ERG are relevant to decision-making

3.15 The company's updated model included a revised health-related quality-of-life analysis which adjusted for age, race, and sex. It also incorporated the response data from the time that quality of life was assessed in the trial ('contemporaneous response'). The updated analysis showed a reduction in quality of life for progressed disease compared with stable disease, which the committee considered to be more plausible than the company's original analysis. However, the committee heard that the company had not accounted for the effect of prior or subsequent treatments on quality of life, which it considered to be implausible. The ERG's main concern with the updated quality-of-life analysis was that pre-progression utility values may have been overestimated, because they were based on a mixture of the contemporaneous response data and on the best overall response of people in TMM1. The ERG explained that its alternative base-case analysis partly corrected this but neither the company's base case nor the ERG's alternative analysis was perfect. The committee concluded that, in the absence of more reliable utility estimates, the results from both the company's base case and the ERG's alternative base case should be considered in its decision-making.

Costs

Extrapolating the duration of treatment data from the TMM1 trial underestimates treatment costs in the model

3.16 The ERG noted that there was a substantial difference between duration of treatment and progression-free survival in the company's model, when the estimates were extrapolated beyond the observed trial data. That is, patients stopped treatment before disease progression. The committee heard that the difference between these estimates increased when the company updated its model with data from the second interim analysis of

TMM1. Over the model's 25-year time horizon, people in the 2 or 3 previous therapies subgroup had ixazomib for only 62% of the time that they spent progression-free. In the lenalidomide plus dexamethaone arm, people had treatment for 69% of the time spent progression-free. The committee was aware that in TMM1 people received ixazomib for 92%, and lenalidomide for 97%, of the time spent progression-free. The committee acknowledged that there are reasons why patients stop treatment before disease progression, for example if they have unacceptable side effects or agree a treatment break with their clinician. However, the committee was concerned that the difference between progression-free survival and time-on-treatment in the model was much greater than the difference seen in the trial on which the model's outcomes were based. The committee heard from the NHS commissioning expert that time-on-treatment is usually the preferred way to model treatment costs. But it understood that the company's method of analysing time-on-treatment was inconsistent with its methods for progression-free survival, which resulted in underestimated treatment costs. It was aware that the ERG had explored the effect of using progression-free survival to model treatment costs instead of time-on-treatment. The committee concluded that extrapolating the duration of treatment data from TMM1 underestimates treatment costs in the model, and that the cost effectiveness of ixazomib would lie somewhere between the estimate based on time-on-treatment data and the estimate based on progression-free survival data.

The costs of treatments taken after disease progression were underestimated in the ixazomib arm

3.17 The updated company model assumed that 66% of patients had further treatment after disease progression, based on data from the second interim analysis of TMM1. The ERG explained that the total cost of treatments taken after progression was the same in the ixazomib arm as the lenalidomide plus dexamethasone arm, even though people having ixazomib lived for 26 weeks longer after stopping treatment than people

having lenalidomide plus dexamethasone. The ERG suggested that this assumption was unrealistic because the number of post-progression treatments taken would be affected by how long a patient lives. The committee saw written statements from clinical experts supporting the ERG's assumption. The committee concluded that the model underestimated the cost of subsequent treatments in the ixazomib arm.

End of life

Survival data from the clinical trial are immature

3.18 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods, focusing on the population who have had 2 or 3 previous therapies. The committee agreed that it could not make reliable conclusions about life expectancy and survival benefit using the results from TMM1, because the survival data are immature and the median overall survival was not reached in either arm of the trial. It did not consider the results of the China continuation study because these were from people who have had 1 or more therapies, which is broader than the population under consideration. With that in mind the committee concluded that is should consider the economic model estimates, recognising that they were based on extrapolating immature data and were therefore uncertain.

Ixazomib does not meet the end-of-life criteria

3.19 The committee discussed the criterion of short life expectancy with current treatment, which is normally less than 24 months. It noted that the modelled overall survival with lenalidomide plus dexamethasone was 3.9 years for people who have had 2 or 3 previous therapies. The committee therefore concluded that ixazomib does not meet the criterion of short life expectancy. The committee acknowledged that this was based on uncertain model extrapolations, but noted that it was consistent with the conclusions about life expectancy from other NICE technology

appraisal guidance for people with multiple myeloma who have had 2 previous therapies. Although ixazomib did not meet the first end-of-life criterion, the committee discussed whether it has the potential to meet the criterion for extension to life, which is normally at least an additional 3 months. The committee considered that the modelled overall survival benefit (1.56 years) and incremental quality-adjusted life year (QALY) gain (between 0.88 and 0.98 QALYs) with ixazomib appeared promising, but agreed that these results were uncertain because most of the modelled improvement in survival occurs during the extrapolation of data beyond the trial period; 94% after the median follow-up period of 23 months, and 88% after the maximum follow-up of 32 months. The committee also recalled the uncertainty about how to extrapolate the trial survival data, and that using the Gompertz curve reduced the incremental survival benefit with ixazomib to 0.99 years (see section 3.14). The company stated that published literature suggests that progression-free survival is a good proxy for overall survival in multiple myeloma, but the committee was not aware of a validated measure to translate progression-free survival benefit into overall survival benefit. The committee agreed that ixazomib has the potential to improve overall survival, but concluded that it did not meet the criterion for extension to life because the estimates were not sufficiently robust. The committee concluded that ixazomib cannot be considered as an end-of-life therapy.

Results including the patient access scheme

Ixazomib is not recommended for people who have had 2 or 3 previous therapies

3.20 The committee discussed the most plausible range of ICERs for ixazomib compared with lenalidomide plus dexamethasone in people who have had 2 or 3 previous therapies. The committee agreed with the changes in the ERG's amended base case, but recalled its conclusion that the company's base-case approach to estimating utility values (which produced an ICER of £125,000 per QALY gained) should be considered alongside the ERG's

amended approach (see section 3.15). The ERG presented 2 versions of its amended base case:

- one using the extrapolation of time-on-treatment data from TMM1 to estimate treatment costs, resulting in an ICER for ixazomib of £140,000 per QALY gained compared with lenalidomide plus dexamethasone and
- one using the extrapolation of progression-free survival data from TMM1 to estimate treatment costs, resulting in an ICER for ixazomib of £202,000 per QALY gained compared with lenalidomide plus dexamethasone.

The committee recalled its conclusion that the most plausible ICER lay somewhere between these 2 estimates (see section 3.16). The committee noted that applying the ratio of time-on-treatment to progression-free survival from TMM1 to the ERG base case using progression-free survival data did not substantially affect the ICER. Therefore the committee concluded that the most plausible ICER was closer to the estimate based on progression-free survival data. The committee noted that the ICERs increased substantially when its preferred assumption about the duration of relative survival benefit of ixazomib was incorporated, that is, the relative benefit lasted undiminished for the maximum trial follow up of 32 months, and then reduced slowly over 5 years (see section 3.13). The ICERs based on this diminishing treatment effect were between £194,000 (costing treatment using time-on-treatment) and £274,000 (costing treatment using progression-free survival) per QALY gained. The committee agreed that the most plausible range of ICERs for ixazomib compared with lenalidomide plus dexamethasone was £125,000 to £274,000 per QALY gained, but closer to the latter. The committee concluded that ixazomib with lenalidomide and dexamethasone could not be recommended as a cost-effective use of NHS resources for treating multiple myeloma in people who have had 2 or 3 previous therapies.

Cancer Drugs Fund

The company proposed consideration of ixazomib in the Cancer Drugs Fund

3.21 The committee was aware that the company was interested in ixazomib being considered for the Cancer Drugs Fund and that it had proposed a commercial offer (the details of which are commercial in confidence and cannot be reported). The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. The committee agreed that there is uncertainty about the clinical benefit of ixazomib on overall survival. It recognised that the survival data are immature and that median survival with ixazomib has not been reached in TMM1. It noted that additional survival analyses from TMM1 will be available by 2019, and that the final survival analyses from another study (the China continuation study) will be available in 2017. The committee noted that the company are required to collect these data, as well as data from a non-interventional observational study, as part of its conditional marketing authorisation.

It is unlikely that ixazomib would satisfy the end-of-life criteria

3.22 The committee agreed that additional data collection has the potential to reduce the uncertainty about the overall survival benefit of ixazomib. So it considered whether there was plausible potential for ixazomib to meet the end-of-life criteria when more mature survival data are available. The committee recalled that the life expectancy of patients having lenalidomide plus dexamethasone in the model was 3.9 years, which exceeds the 24 months stated in the end-of-life criteria. The committee discussed whether it could apply its discretion for this criterion by considering the proportional gain in survival compared with the prognosis based on the modelled estimates. The committee noted that the life expectancy was substantially better than the 24 months stated in the end-of-life criteria, and agreed that an extension to life of 1.56 years did not represent an exceptional proportional gain. The committee agreed that

further data collection would reduce the uncertainty in the survival benefit of ixazomib, but did not see any plausible potential for ixazomib to satisfy the criteria for end of life based on the current estimates of life expectancy and proportional gain in survival with ixazomib.

Ixazomib does not meet the criteria to be included in the Cancer Drugs Fund

3.23 The committee understood that the commercial offer proposed by the company improved the cost effectiveness of ixazomib. But it was aware that the company's revised base-case ICER was above the range normally considered to be a cost-effective use of NHS resources when the end-of-life criteria have not been met. The committee noted that the most plausible range of ICERs, including its preferred assumptions, was substantially above the range normally considered to be a cost-effective use of NHS resources. The committee agreed that further data collection would reduce the uncertainty about the survival benefit of ixazomib, but did not see any plausible potential for ixazomib to satisfy the criteria for routine use based on the company's proposed commercial offer. The committee concluded that ixazomib does not meet the criteria to be included in the Cancer Drugs Fund.

Other factors

The committee did not identify any other factors that would affect its recommendations

3.24 No equality or social value judgement issues were identified.

3.25 The Pharmaceutical Price Regulation Scheme (2014) payment mechanism was not relevant in considering the cost effectiveness of ixazomib.

3.26 There were no additional health benefits that had not already been captured in the QALY calculations. The patient expert noted that most of the treatments used to manage multiple myeloma involve injections and infusions, therefore patients would welcome another oral treatment option.

The committee acknowledged that the oral administration of ixazomib with lenalidomide and dexamethasone is a benefit, particularly for older or frail patients who find it difficult to travel to hospital for treatment. However the main comparator, lenalidomide plus dexamethasone, is also an oral regimen.

Conclusion

3.27 The committee could not recommend ixazomib, with lenalidomide and dexamethasone, for treating multiple myeloma in adults who have had at least 1 previous therapy.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive in December 2019. This review date reflects the deadline for Takeda to submit the results of new and ongoing studies to the European Medicines Agency, including the final overall survival analysis from the TMM1 trial. Providing these data is an obligation of the conditional marketing authorisation for ixazomib. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
August 2017

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sophie Cooper
Technical Lead

Raisa Sidhu
Technical Adviser

Kate Moore
Project Manager

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